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# Influence of mental stress on fibrinogen, von Willebrand factor and tissue-type plasminogen activator antigen

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**Summary** To investigate the effect of mental stress on fibrinogen, von Willebrand factor (vWf) and tissue-type plasminogen activator antigen (t-PA:ag), blood samples were obtained before (ca. 10:45 AM) and after (ca. 1:30 PM) a period in which subjects were exposed to 3 mental stressors. Subjects were 61 males and 114 females aged 30-65 years. Fibrinogen, vWf and t-PA:ag decreased significantly during these mental stress tasks for both males and females. The decrease in fibrinogen and vWf may have largely been caused by a comparable decrease in hematocrit. The much stronger decline in t-PA:ag may have been due to a circadian rhythm. At any rate, neither males nor females showed an increase in fibrinogen, vWf or t-PA:ag. Probably the expected rise in coagulation and fibrinolysis in response to mental stressors has been overruled by circadian rhythms and/or factors influencing plasma volume.

## INTRODUCTION

Research into changes in coagulation and fibrinolysis in response to mental stress is sparse. Palmblad et al.<sup>1</sup> observed in 16 females a decrease in several coagulation factors, including factor V, VIII, IX and fibrinogen, in response to a 77-hours vigil. No change in fibrinolytic activity was detected. In response to a bleeding time test, Urano et al.<sup>2</sup> found a decrease in total and free plasminogen activator inhibitor 1 (PAI-1) but no change in t-PA levels in 41 male students. Jern et al.<sup>3</sup> investigated the effect of two short-term laboratory stress tasks (duration: 20 min.) in 10 males. An increase in t-PA activity (54%), t-PA:ag (32%), fibrinogen (8%), vWf (29.5%) and both factor VII (25.5%) and factor VIII (73.5%) coagulant activity were observed. These results were confirmed in a later study of the same group.<sup>4</sup> In 9 females, exposed to the same set of stress tasks, significant increases in t-PA activity (50%), t-PA:ag (12%), vWf (9%) and fibrinogen (9%) were found. In contrast to the male group, no significant changes in factor VII coagulant activity were seen. Factor VIII coagulant activity was not assessed in the females. In both males and

females a slight but significant increase in hematocrit was observed (3% and 2.4% respectively). PAI-1 levels did not change.<sup>3,4</sup>

Results between studies are hardly comparable since duration and type of stress widely differed. Using the same stressors, Jern et al.<sup>3,4</sup> obtained relatively consistent results, irrespective of the sex of investigated subjects. Both studies indicate that activity of both coagulation and fibrinolysis increases in response to mental stress. Drawback of the latter studies, however, is the small number of subjects. In an effort to replicate results from Jern et al.<sup>3,4</sup> in larger samples, this study investigated the effect of mental stress on fibrinogen, vWf and t-PA:ag and possible sex differences therein. To that end, in 61 males and 114 females blood samples were obtained before and after a series of mental stress tasks.

## MATERIALS AND METHODS

### Subjects

This study was part of a larger project in which cardiovascular risk factors were measured in middle-aged twins.<sup>5</sup> Subjects consisted of 61 males (age:  $42.1 \pm 5.5$ ) and 114 females (age:  $45.5 \pm 7.0$ ). Informed consent was obtained from all subjects.

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## Procedure

Subjects arrived at the laboratory at about 10.00 AM after an overnight fast. At about 10.45 AM a prestress blood sample was collected by venipuncture. Subjects then filled in questionnaires and practised the stress tasks. Subsequently a set of three mental stress tasks were performed: a choice reaction time (RT) task, a speeded mental arithmetic (MA) task and a tone avoidance (TA) reaction time task.<sup>6</sup> Each mental task condition lasted 8.5 minutes and was preceded by a rest period of three minutes. Directly after finishing the third mental stress tasks (ca. 1:30 PM), a second blood sample was obtained. Sequence of events was: prestress blood sample, practice sessions of tasks & questionnaires, rest1, RT, rest2, MA, rest3, TA, poststress blood sample.

## Blood sampling and biochemical assays

Blood was collected by venipuncture, using Vacutainer tubes (Becton-Dickinson) containing sodium-EDTA. Tubes were placed on ice and centrifuged promptly (30 minutes, 2000g) at 4°C to separate plasma from cells. Aliquots of plasma were snap-frozen using liquid nitrogen and stored at -20°C until processing. For determination of hematocrit, unheparinated capillaries were filled with EDTA blood and centrifuged (Hawksley centrifuge) for 6 minutes at 11000 rpm. Fibrinogen was determined by enzyme-linked immunosorbent assay (ELISA; Organon Teknika, Turnhout, Belgium) as described by Hoegee-de Nobel et al.<sup>7</sup> Von Willebrand Factor was assessed by ELISA, using polyclonal antibodies (Dako; Cat.No. A082). Determination of t-PA:ag was done by ELISA (Organon Teknika, Turnhout, Belgium) as described by Bos et al.<sup>8</sup>

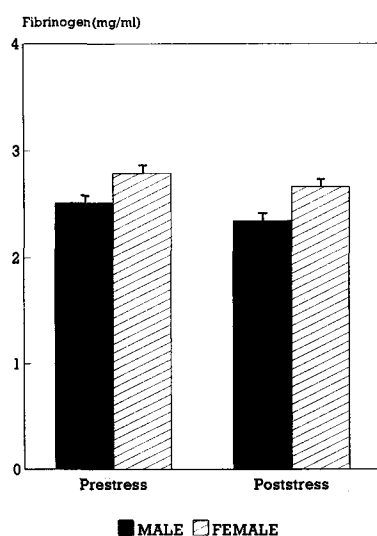


Fig. 1 Prestress and poststress values of fibrinogen (mean  $\pm$  SEM) in males and females.

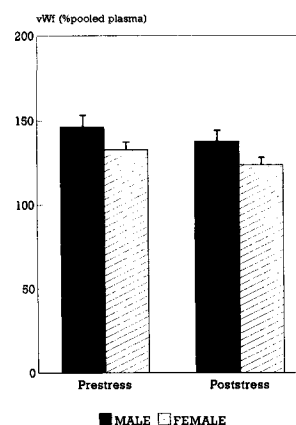


Fig. 2 Prestress and poststress values of vWf (mean  $\pm$  SEM) in males and females.

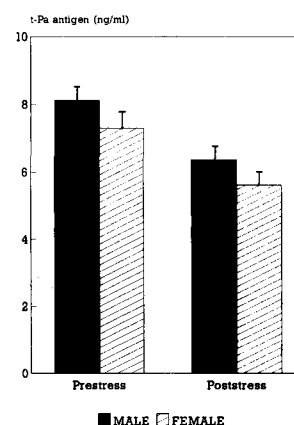


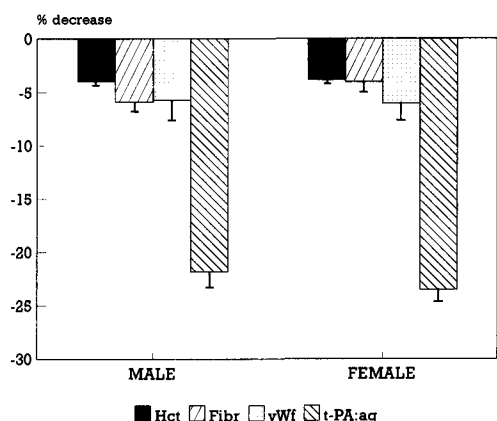
Fig. 3 Prestress and poststress values of t-PA:ag (mean  $\pm$  SEM) in males and females.

## Statistical analysis

To test for the effect of sex and stress, MANOVA was used. Fibrinogen, vWf, t-PA:ag and hematocrit were analyzed as dependent variables with stress as a within factor and sex as a between factor.

## RESULTS

Figures 1 to 3 show concentrations of fibrinogen, vWf and t-PA:ag before and after performance of the stress tasks, for males and females separately. MANOVA demonstrated a significant main effect of stress for fibrinogen, vWf and t-PA:ag (all  $p$ 's < 0.001). All variables showed a decrease from the prestress to the poststress blood sample. Hematocrit, however, also showed a significant decrease ( $p$  < 0.001). Furthermore, a main effect of sex was found for fibrinogen ( $p$  < 0.01) and vWf ( $p$  < 0.05). Fibrinogen was higher in females, vWf higher in males. No interaction effects between sex and stress were observed, which means that the pre- to poststress decrease does not differ between the sexes.



**Fig. 4** Percentual change (mean  $\pm$  SEM) in hematocrit (Hct), fibrinogen (fibr), vWf and t-PA:ag from pre- to poststress.

In figure 4 the percentual change from pre- to poststress in hematocrit (males:-4.0%; females:-3.8%) , fibrinogen (males:-5.9%; females:-4.0%), vWf (males:-5.7%; females:-6.1%) and t-PA:ag (males:-21.8%; females:-23.5%) is shown. The percentual decline of hematocrit almost equals the decline of fibrinogen and vWf. The decline in t-PA:ag, however, is much larger.

## DISCUSSION

This study investigated the effect of mental stress on fibrinogen, vWf and t-PA:ag. All three variables decreased significantly from the prestress to the poststress blood sample. The response did not differ between males and females. These results were in contrast with the studies from Jern et al.<sup>3,4</sup> who, in both sexes, observed substantial increases in fibrinogen, vWf and t-PA:ag, which could not have been due to the only slight increase in hematocrit. In our study, however, the percentual decline in hematocrit almost equaled the decline in fibrinogen and vWf. This finding indicates that the decrease in fibrinogen and vWf is probably caused by a comparable decrease in hematocrit, which implicates a rise in plasma volume. The change in t-PA:ag could not be explained by the change in hematocrit, as t-PA:ag showed a much stronger decline. In a study on the effect of sampling time on fibrinolytic variables and fibrinogen, Eliasson et al.<sup>9</sup> observed a decline of 21% for males and 23% for females from 7.00 AM to 2.00 PM. These values are remarkably similar to our findings. Therefore it cannot be ruled out that the decrease in t-PA:ag from the time of the prestress blood sample (ca. 10:45 AM) to the poststress sample (ca. 1:30 PM) is caused by a circadian rhythm.

If an increase comparable to the results from Jern et al.<sup>3,4</sup> had occurred in our data, such an increase in combination with the opposing effects of the circadian rhythm and the

fall in hematocrit, would have resulted in relatively unchanged levels of fibrinogen, vWf and t-PA:ag. The decline as observed in this study therefore suggest that the set of mental stress tasks had a negligible influence on fibrinogen, vWf and t-PA:ag. It can thus be concluded that in contrast to results from Jern et al.<sup>3,4</sup>, for neither males nor females evidence was found for an increase in activation of coagulation and fibrinolysis in response to mental stress.

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